REMARKS

Exemplary support for the claim amendments is as follows:

Claims 1 and 19 - page 6, line 7 – page 7, line 5; paragraph bridging pages 8 and 9; and page 14, lines 10-15.

Claim 11 – page 17, line 15 – page 18, line 4; page 16, line 31 – page 17, line 9.

Claims 20, 21 and 31 – page 6, line 7 – page 7, line 5; page 10, line 22 – page 11, line 1; claim 32 – see also paragraphs 71 and 73 of US 2004/0180396, corresponding to WO 00/22439, referred to in the cited paragraphs of the specification, which paragraphs state that the RIA's manufacturer's instructions were followed and which instructions required an extraction step believed to contribute to the RIA's problems (see also the discussion on page 16 below).

Claim 22 – page 4, lines 10-25.

Claim 23 – page 6, line 7-page 7, line 5.

Claim 24 – page 14, lines 16-25.

Claim 25 – page 15, line 10 – page 16, line 29.

Claims 26 - 29 – page 6, line 7 – page 7, line 5.

Claim 30 – paragraph bridging pages 8 and 9.

Claims 20, 21 and 31 – page 5, line 29 – page 7, line 5. See MPEP § 2173.05(i) regarding the propriety of the involved negative limitation.

The foregoing claims are patentable in view of the following facts established in the current specification. The various claims represent different ways of

distinguishing the cited Bergmann et al reference. All encompass non-obvious subject matter.

The level of adrenomedullin (AM) release in a human (page 3, lines 5-19; page 9, lines 12-27, etc.) is known to be correlated with a variety of diseases, including sepsis and others. See page 3, lines 20-28; page 4, lines 5-28; page 9, lines 12-27; page 14, lines 16-25; and page 29, lines 10-16, for example. ("AM" and "ADM" are used interchangeably herein to mean adrenomedullin). Thus, the level of AM release is per se a conventional parameter which is quite useful for diagnostic purposes relating to a variety of diseases. However, it is quite difficult to obtain reliable direct measurements of this peptide. See the paragraph bridging pages 7 and 8 of the specification for a discussion of some of the reasons why this is true.

> The data for most research work were obtained using RIAs which were based on competition of AM with a labeled marker peptide for a common AM binding site of an antibody. The respective RIAs were often individual developments, and various antibodies and peptides were employed, making a quantitative interassay comparison of the measured results obtained more difficult (cf. for example 10). Moreover, recent research results had shown that there are various forms of AM (with or without C-terminal glycine residue), to which different activities could be assigned (cf. (2) and, for example, (5)). The discovery of a binding protein (cf. 11) for AM led to a further complication of the situation – both the present or absent glycine residue and the absent or present complexing of AM by its binding protein can influence the determination of AM as a function of the respective assay in an unpredictable manner. These circumstance set high requirements with regard to a valid immunoassay for AM which is suitable for routine investigations: for such an assay, it is necessary to find suitable antibodies which bind to those AM regions which are not occupied by the binding protein, if there are such regions at all. Alternatively, it is necessary to carry out a preceding step for the liberation and separation of the binding protein from AM, the influence of such a step on

> the stability of the AM and/or the measured values obtained being difficult to estimate. The fact that, in addition to the complete AM, different AM partial peptides are also found physiologically and appear to play a role in the overall physiological process further complicates the provision of a valid immunoassay and the comparability of the measured values appearing in the literature.

This invention involves the discovery of a reliable and accurate way to determine a parameter directly correlated with the level of AM release in a patient, instead of AM itself. In essence, this involves the discovery that a particular peptide fragment, having a sequence existing in the precursor protein from which AM is derived, is per se circulating in the blood and is directly correlated with the level of AM release. Measurement of levels of this particular fragment avoids the problems associated with direct measurement of AM. This fragment is termed in the claims "mid-regional partial peptide." It has SEQ. ID NO: 3. It is composed of amino acids 45-92 numbered in accordance with the complete sequence (SEQ ID NO: 1) of preproadrenomedullin, the mentioned precursor protein. These facts are established throughout the specification. See, e.g., page 9, line 21 – page 10, line 6 and page 14, lines 10-25, among others. (For convenience, a sequence chart is attached, demonstrating the relationships among AM, pro-AM, prepro-AM and the partial peptide, "MR-proADM." These relationships are disclosed in the specification at page 2, line 5 – page 3, line 3).

As the examiner notes, in paragraph 73, Bergmann et al states: "for the determination of pro-ADM (same as pro-AM used herein), the Pro-Adrenomedullin 45-92 (human) RIA kit" was used. The kit was from DRG, a company further

identified in paragraph 71 of Bergmann et al. As discussed in the current specification, e.g., the paragraph bridging pages 6 and 7, using the mentioned kit, an elevated level in sepsis patients of "pro-adrenomedullin" of about 2X that in healthy humans was measured. See also Figure 7 of Bergmann et al. However, as discussed in the mentioned paragraph of this application, it is known that levels of AM release in the case of sepsis patients are on the order of 12X the normal level. This level is so much higher than the order of magnitude of about 2X the normal level which was observed in Bergmann et al., that skilled workers would necessarily assume that the Bergmann et al. approach does not provide a reliable correlation of AM release levels in a patient sufficient for commercial diagnosis of disease.

This is somewhat confusing at first sight because Bergmann appears to use the same sequence portion for its assay ("Pro-Adrenomedullin 45-92 (human) RIA kit") as is recited in the claims of this application (amino acids 45 – 92 of prepro-AM). Yet, in contrast, for the assays of this invention, excellent correlation with AM release levels is established. However, upon closer study, it is clear that Bergmann et al is not disclosing the assay of this invention.

Note that Bergmann's commercial RIA kit refers to the 45-92 amino acid region of pro-adrenomedullin. A skilled worked would interpret this using nomenclature wherein the first amino-acid of the pro-adrenomedullin peptide would be designated as amino acid no. 1, as is the case for any protein unless indicated otherwise. As can be seen in the lower portion of the attached chart, the nomenclature used by Bergmann et al is such that its amino acids 45-92 based on pro-AM numbering correspond to amino acids 66-113 using the nomenclature of this

application, which is based on the prepro-AM sequence numbering. The difference resides in the lack of the leader sequence in pro-AM. See the accompanying chart.

The forgoing facts are further supported by Table 2 of Bergmann, which states the "N-terminus" of pro-adrenomedullin begins with the two amino acids Ala Arg. Reference to SEQ ID NO: 1 of the current application or the attached chart shows these two amino acids indeed to be those which are at the beginning ("N-terminus") of pro-adrenomedullin. The "beginning" of a protein, of course, is the location of its first amino acid at its N-terminus. Thus, the numbering in Bergmann is consistent with the first amino acid of pro-AM being given the number, 1, and not, as in this application, being given the number corresponding to its position in the precursor prepro-AM molecule.

Thus, the specific target fragment of this invention (45-92 of prepro-AM) does not have the same sequence as the region mentioned in Bergmann et al. The two merely overlap. Consequently, a skilled worker based on Bergmann et al would not necessarily design an assay in a manner which would reliably detect the specific fragment of this invention because the sequence and the target (pro-ADM) taught by Bergmann et al. are not the same. In fact, its target is a much longer peptide (pro-AM) than that targeted by this invention. Note Bergmann's Paragraph 73, "for the determination of pro-ADM..." Pro-adrenomedullin has a length of 164 amino acids as also explicitly stated in Table 2 of Bergmann. This length is to be contrasted with the much shorter circulating fragment underlying the current invention which is 48 amino acids long.

Thus, reading Bergmann et al, a skilled worker cannot know whether its RIA assay detected epitopes within the fragment sequence of this invention or not. She also is not taught to design assays which target only amino acids within the fragment sequence of this invention. Rather, a skilled worker would learn in Bergmann to target pro-ADM sequences in general. Moreover, Bergmann et al teaches a skilled worker to employ procedures consistent with a protein of a length of 164 amino acids. Sample preparation (extraction) would thus be different from that which would be employed for a much shorter peptide of only 48 amino acids. (In fact, in following the recommended sample preparation/extraction procedures accompanying the DRG kit used for the RIA of Bergmann et al, its assignee (same as for this application) believes that the original amounts of the mid-regional partial peptide inherently contained in the sepsis samples were incompletely extracted due to these procedures. The latter optimized the extraction of the much longer protein target of the commercial DRG kit which was pro-AM. This, it is believed, contributed to the inherent measurement of only a low level thereof in the sepsis patients, only 2X that over normal levels).

What is clear is that Bergmann et al teaches a different AM release detection strategy from that of this invention. It is not surprising then that it reports results which are different from those of this invention, showing that it did not conduct an assay of this invention. It does not anticipate this invention. It was not heretofore known that the mid-regional partial peptide even existed in human blood. Not having taught the targeting of the mid-regional partial peptide discussed for the first time in this invention, it also cannot render this invention obvious.

In view of these facts, the current claims are believed to properly recite novel and non-obvious subject matter based on the described new discovery of the mid-regional partial peptide (referring to independent claims):

Claims 1, 19 and 31

Because the sequence region of the prior art merely overlaps with that of this invention, there is no teaching to use in an assay a monoclonal or polyclonal antibody specific only to the mid-regional partial peptide.

Claims 20, 21, 31 and 32

These claims completely eliminate the teaching in Bergmann et al. of using its RIA.

Claims 22-24

These specify that the level of the mid-regional partial peptide which is measured is that circulating in a patient. Clearly, this is not the case in Bergmann et al. who measured too low levels as established by the data in this application.

Claim 25

Sandwich assays wherein at least two antibodies are specific to the mid-regional partial peptide are not taught or suggested by Bergmann et al.

Claims 26 - 29

Bergmann et al. gives no hint at all to detect pro-AM in any way for any purpose other than diagnosing sepsis.

(It is to be noted that the Bergmann et al. disclosure is legitimate and accurate for what it states and does support its own claims. It simply cannot be reasonably

extrapolated by a skilled worker to arrive at any of the subject matter claimed in this application.)

In view of the foregoing, it can be seen that the conventional technologies disclosed in the cited secondary references cannot possibly suggest any of the claimed subject matter in combination with Bergmann et al, because of the distinctions established above. Thus, the examiner's allegations based on these references are moot. No agreement with them is to be implied.

All rejections based on Bougueleret (having an earliest possible effective date of April 25, 2003) are untenable at least in view of the certified English translation of priority document EP 103 16 583.5 of April 10, 2003, being filed herewith.

The double patenting rejections are to be held in abeyance until they can be dealt with non-provisionally, i.e., when the language of allowable claims is agreed upon in this application.

A copy of Ueda et al. is being filed.

Respectfully submitted,

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